

Comparison of Clinical Features between Typical and Atypical Takotsubo Cardiomyopathy: A Single Center, Retrospective, Case-Controlled Study

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Background: The incidence and possible differences between typical and atypical Takotsubo cardiomyopathy (TTC) in Taiwanese patients have not yet been assessed.

Methods: We reviewed the records of 2171 patients who underwent left heart catheterization for suspected acute coronary syndrome (ACS) between January 2003 and March 2011 to identify TTC. Demographic, clinical presentations, laboratory data, and electrocardiographic, echocardiographic and angiographic findings were assessed in all patients.

Results: We found that fourteen patients had typical TTC, and six had atypical TTC. There were no differences in the clinical presentations, ejection fraction and in-hospital course of illness between patients with typical TTC (the TT group) and patients with atypical TTC (the AT group). However, the patients in the AT group were relatively younger than those in the TT group (mean ages 60 vs. 73 years, respectively, $p = 0.018$), and fewer patients had hypertension in the AT group than in the TT group (33% vs. 86%, respectively, $p = 0.037$). In electrocardiography, ST segment elevation was noted less frequently in the AT group than in the TT group (33% vs. 86%, respectively, $p = 0.037$).

Conclusions: Atypical TTC and typical TTC may be the same syndrome with different manifestations. They seemed to have different patient characteristics and electrocardiographic changes.

Key Words: Acute coronary syndrome • Takotsubo cardiomyopathy • Transient left ventricular apical ballooning

INTRODUCTION

Takotsubo cardiomyopathy (TTC), also known as transient left ventricular apical ballooning syndrome or stress cardiomyopathy, was first described in the Japanese literature in 1991 by Dote et al.¹ The true incidence

of TTC in Taiwan is unknown, but a recent study revealed a prevalence of 0.9% of patients presenting with ACS in one center.² The syndrome is characterized by chest symptoms associated with electrocardiographic (ECG) changes (ST segment elevation or T-wave inversion with QT prolongation) and mild elevation of cardiac enzymes. Typically, left ventriculogram demonstrates hypo or akinesis from the mid-portion of the anterior wall to the apex, and hyperkinesis of the basal area. The clinical presentation mimics ACS. However, no evidence of coronary artery stenosis is seen on angiography, and the left ventricular dysfunction can completely regress. Recently, several atypical forms of Takotsubo cardiomyopathy, known as “mid-ventricular ballooning syndrome”, or “inverted Takotsubo” have been reported.

Although the prevalence and clinical features of

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Takotsubo cardiomyopathy (TTC) in Taiwanese patients have previously been reported,² the incidence and possible differences between patients with typical and atypical TTC have not yet been assessed. In the present study, we evaluated and compared 14 patients with typical TTC and six patients with atypical TTC.

METHODS

Patients who were admitted with acute coronary syndrome to our institution from January 2005 to March 2011 were screened retrospectively. The inclusion criteria for the study were: (1) unstable angina with ST depression of at least 1 mm or T-wave inversion with normal enzymes; (2) acute myocardial infarction without ST elevation; and (3) acute myocardial infarction with ST elevation. The exclusion criteria were: (1) suspected or proven acute myocarditis; (2) suspected or proven non-cardiac pathology (such as pheochromocytoma crisis, pulmonary embolism or aortic dissection). TTC was identified in these patients according to the following modified Mayo Clinic Criteria for the clinical diagnosis of TTC:³ (1) transient hypokinesis, akinesis, or dyskinesis of the left ventricle (LV) and mid-segments with or without apical involvement and with regional wall motion abnormalities extending beyond a single epicardial vascular distribution; (2) absence of significant coronary stenosis (more than 50% of the luminal diameter) or angiographic evidence of acute plaque rupture; (3) new ECG abnormalities (ST-segment elevation and/or T-wave inversion); and (4) absence of pheochromocytoma or myocarditis. Demographic characteristics, clinical histories, preceding stressors, presenting symptoms, laboratory data, ECG, echocardiographic and angiographic findings were collected from the patients' medical records. Echocardiography studies were performed in a standard fashion to assess LV wall motion abnormality at presentation and at follow-up in all patients. The LV ejection fraction was measured using a modified Simpson's method. Survival follow-up data were prospectively collected through clinical outpatient visits or telephone calls to the patients or relatives. Major clinical events were cardiac death and re-hospitalization due to recurrence of this syndrome. The study fully complied with the Declaration of Helsinki and was

approved by our local Research Ethics Committee.

Statistics and analysis

All data were analyzed using SPSS for Windows version 12.0 (SPSS, Chicago, IL, USA). Continuous variables were expressed as mean \pm standard deviation (SD) and range. Categorical data were presented as absolute values and percentages. Patients in the typical and atypical TTC groups were compared using Fisher's exact test for categorical parameters and unpaired t-tests for continuous variables (Table 1). A p value less than 0.05 was considered to be statistically significant.

RESULTS

Among the 2171 patients with suspected ACS, 20 patients met the diagnostic criteria for TTC, giving a prevalence of 0.9%. Fourteen patients (13 women) had typical TTC (the TT group), and six patients (all women) had atypical TTC (the AT group). A comparison of the clinical features between the groups is summarized in Table 1. There were no significant differences between groups with regards to sex and preceding stressors. Compared with the TT group, the AT group was younger (mean age 60 years in AT group vs. 73 years in TT group, $p = 0.018$). The incidence of coronary risk factor or comorbidities such as type 2 diabetes mellitus, hyperlipidemia, smoking and end stage renal disease were not significantly different between the two groups. The prevalence of hypertension was particularly low in the AT group (33% vs. 86% in the TT group, $p = 0.037$). In most cases, the initial presentation was chest pain, followed by dyspnea and syncope.

The incidence of pulmonary edema and ventricular tachycardia were not significantly different between the two groups. Eight patients developed acute pulmonary edema requiring diuretics and one patient required ventilator support. One patient required an intra-aortic balloon pump for treatment of unstable hemodynamics. Three patients developed ventricular tachycardia and two patients required electrical cardioversion. All of the three patients had only one episode of sustained ventricular tachycardia and did not recur after management.

Initial ECG showing ST-segment elevation was apparent in two patients with atypical TTC (33%); however,

Table 1. Comparison of the clinical features between patients with typical and atypical Takotsubo cardiomyopathy

	Typical (n = 14)	Atypical (n = 6)	p value
Age	73 ± 10	60 ± 11	0.018
Female	13 (93%)	6 (100%)	1
Hypertension	12 (86%)	2 (33%)	0.037
Type 2 diabetes mellitus	5 (36%)	4 (67%)	0.336
Hyperlipidemia	4 (29%)	2 (33%)	1
Smoker	1 (7%)	0 (0%)	1
End-stage renal disease	2 (14%)	0 (0%)	1
Chest pain at presentation	9 (64%)	4 (67%)	1
Dyspnea at presentation	4 (29%)	1 (17%)	1
Syncope at presentation	1 (7%)	1 (17%)	0.521
Physical stress or acute medical illness	8 (57%)	3 (50%)	1
Emotional stress	2 (14%)	2 (33%)	0.549
Pulmonary edema	6 (43%)	2 (33%)	1
Ventricular tachycardia	2 (14%)	1 (17%)	1
ST segment elevation	12 (86%)	2 (33%)	0.037
Maximum QTc (ms)	533 ± 58	520 ± 75	0.692
Peak CK (IU/L)	358 ± 215	371 ± 278	0.916
Peak Troponin-I (ng/mL)	8.72 ± 7.14	4.10 ± 4.19	0.160
Initial LVEF (%)	40 ± 11	40 ± 5	0.972
Follow-up LVEF (%)	65 ± 6	66 ± 5	0.734
Long wrap LAD	3 (21%)	1 (17%)	1
Hospital day	16 ± 19	8 ± 4	0.304

CK, creatine kinase; LAD, left anterior descending artery; LVEF, left ventricular ejection fraction; QTc, corrected QT interval.

this phenomenon resolved in both patients within a few days. All of these patients developed T-wave inversion. Q-wave was not apparent in any of our patients. The maximum corrected QT interval calculated using Bazett's formula was prolonged (> 450 milliseconds) in both groups (mean 533 ± 58 vs. 520 ± 75 milliseconds). The ECG findings were not significantly different between the groups with regard to the frequency of T wave inversion, and corrected QT interval. However, the presence of ST-segment elevation was significantly less frequent in the AT group compared to the TT group (33% vs. 86%, $p = 0.037$). All patients developed ST-segment elevation in precordial leads, and concomitant ST-segment elevation in the inferior leads was found in one patient from each group.

The peak values of cardiac enzymes were not significantly different between the groups, with the TT group having the mean peaks of creatine kinase and troponin I levels of 358 ± 215 IU/L and 8.72 ± 7.14 ng/mL, respectively, and 371 ± 278 IU/L and 4.10 ± 4.19 ng/mL, respectively, in the AT group. Baseline and follow-up echocardiography were performed on all pa-

tients. The mean LV ejection fraction in AT patients increased from 40 ± 5% upon admission to 66 ± 5% at follow-up (Table 1). As with the AT group, all patients in the TT group had recovered from wall motion abnormalities at follow-up. No pressure gradients or instances of LV outlet obstruction were observed in any patients.

Coronary angiography was performed less than 48 hours after symptom onset in all patients. Fourteen patients had normal coronary arteries, and six patients had insignificant stenosis of any coronary artery. Three patients (21%) in the TT group and one patient in the AT group had a long wrap-around left anterior descending coronary artery.

Angiographic evidence of plaque rupture, or intracoronary thrombus formation was not observed in any of our patients. No provocation tests or endomyocardial biopsies were performed. All patients underwent concomitant LV angiography to assess the LV wall motion abnormality after coronary angiography. None of our patients underwent follow-up LV angiography. Fourteen patients presented with a typical pattern of TTC, i.e. akinesis or hypokinesis of the mid-to-distal portion of

the LV chamber. Six patients presented with an atypical TTC including five patients who presented with mid-ventricular ballooning without involvement of the LV apex, and one patient who presented with inverted TTC (akinesis of the basal and mid-ventricular segments, with hyperkinesis of the apical segments). Representative left ventriculography images are shown in Figure 1.

Initially, most patients were treated for ACS with medication including nitrates, beta-blockers, aspirin, clopidogrel, and heparin unless they had contraindications to these medications. Inotropic agents were administered to six patients (30%), and temporary pacemakers were inserted in two patients (10%). Management and clinical outcomes were not significantly different between the groups. Patients in the AT group had a mean of eight days of hospitalization. All patients were discharged in an improved state and no recurrence of symptoms or major adverse cardiac events occurred during follow-up (43.3 ± 28.3 months).

DISCUSSION

The prevalence and clinical features of Takotsubo

cardiomyopathy (TTC) in Taiwanese patients have previously been reported. However, the incidence and possible differences between patients with atypical and typical TTC have not yet been assessed. One review of relevant studies suggested that TTC accounts for 0.7 to 2.5% of patients presenting with a suspected ACS.⁴ The prevalence of TTC in our cohort of Taiwanese patients presenting with ACS was 0.9%. In the present study, atypical TTC was observed in 6 of 20 patients (30%), compared to 14 of 20 patients (70%) with typical TTC. Patients suffering from atypical TTC may have a clinical presentation very similar to that of typical TTC, in that the initial presentations did indeed mimic ACS. In both groups, most patients improved rapidly and recovered LV systolic function after medical treatment. A female preponderance was also noted in both groups; however, the patients were younger and the incidences of hypertension were lower in the AT group compared to the TT group. In addition, the presence of ST-segment elevation was significantly less frequent in the AT group compared to the TT group.

Kurowski and colleagues reported that the atypical type was seen in 40% of patients with TTC, and that no differences in demographics, clinical findings, angio-

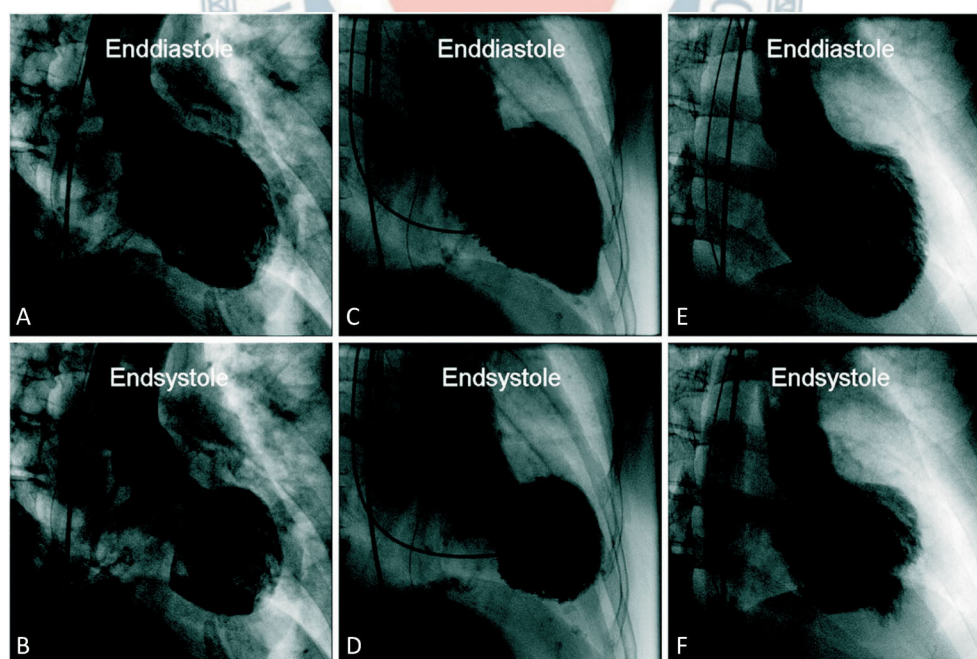


Figure 1. End-diastolic and end-systolic frames of three patients with TTC: Panels A and B represent typical TTC, Panels C and D are examples of the mid-ventricular variant. Panels E and F are examples of inverted TTC (akinesis of the basal and mid-ventricular segments, with hyperkinesis of the apical segments).

graphic findings, laboratory parameters, or outcomes were found between these patients and patients with typical TTC.⁵ However, Hahn et al. reported that patients with non-apical LV ballooning shared the same clinical features as those with the typical form of apical ballooning, but tended to be younger and have a lower incidence of cardiogenic shock, pulmonary edema and T-wave inversion.⁶ Schneider et al. presented their experience with the atypical form of TTC and also concluded that patients with atypical TTC were also younger than patients with typical TTC.⁷ In the present study, the mean age was also lower in the AT group than in the TT group. Thus, an atypical TTC may occur in younger patients compared to those with typical TTC.

The prevalence of hypertension in the TT group was about 86% in our study, which is higher than in previous studies.^{4,8} However, a similar prevalence was found in a recent report, and the age distribution of the patients in this report was more consistent with our study.⁹ In the present study, we observed that the percentage of hypertension in patients with atypical TTC was lower than that in patients with typical TTC. Hahn et al. reported the same findings that atypical TTC was associated with a lower prevalence of hypertension compared with typical TTC.⁶ However, the cause of the lower prevalence of hypertension in patients with atypical TTC is unknown, and it may only be because these patients tend to be younger than patients with typical TTC.

The ECG findings associated with TTC are numerous, but the most common abnormality is ST segment elevation. Typically, the elevation is present in the precordial leads, but it may also be seen in the inferior or lateral leads, nonspecific T-wave abnormality, new bundle branch block, and in some cases, a normal ECG may be the finding at presentation.^{3,4} In the present study, ST elevation occurred less frequently in the AT group than in the TT group. Because the ST-segment elevation was transient, there is a possibility that ST-segment elevation was not recorded in patients with atypical TTC due to a delayed time interval from symptom onset to presentation, T-wave inversion in all patients was subsequently found. It has been suggested that ST-segment abnormalities in patients with atypical TTC resolve more rapidly than in those with typical TTC. A recent study by Dib et al. concluded that the ECG features at presentation do not correlate with the magnitude of ventricular

dysfunction or long-term outcomes.¹⁰ Thus, the ECG findings in patients with TTC do not provide significant prognostic information.

The exact cause of TTC is still not well understood. Enhanced sympathetic activity may play a central role in the pathophysiology and regional differences in adrenergic sensitivity or innervation could then explain the different clinical presentations with other regions of hypokinesia.¹¹⁻¹³ Other mechanisms for reversible cardiomyopathy have been proposed, including multi-vessel epicardial spasm, microvascular dysfunction and plaque rupture followed by spontaneous thrombolysis in a long wrap-around left anterior descending (LAD) coronary artery.¹⁴⁻¹⁷ In our study, only three patients with typical TTC had a long wrap-around LAD. Furthermore, this mechanism would be opposed by the atypical form of TTC.

In keeping with previous reports,^{3,4,8} the prognosis of patients who had TTC in our study was generally favorable, however severe complications such as ventricular arrhythmia, pulmonary edema, ventricular rupture and cardiogenic shock have been reported. There were no significant differences between patients with typical and atypical TTC with regards to the frequency of pulmonary edema or ventricular tachycardia in our study, and supportive therapy invariably led to a spontaneous recovery. The ejection fraction at presentation was equally decreased in both groups by the same amount, and had normalized in all patients at follow-up. No patient died either during hospitalization or follow-up. In accordance with published reports,^{3,4,8} our findings indicate that patients with TTC have a favorable outcome once they have recovered from the acute stage.

Study limitation

This study was performed as a retrospective analysis of data from a single institution and the small sample size of the study group may obscure potentially significant differences. Furthermore, ECG and echocardiographic examinations were not scheduled during follow-up; hence, we could not precisely assess the time course of the ECG changes and normalization of LV dysfunction. The other significant limitation is due to the absence of systemic investigation of possible etiologic mechanisms such as catecholamine measurements, magnetic resonance imaging, or endovascular analysis

with recent technologies such as intravascular ultrasound or angiography.

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